IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 20, Issue 4 Ser.14 (April. 2021), PP 11-16
www.iosrjournals.org

The Role and Importance of Lipoproteins, Vitamin D3, Vitamin K and Magnesium in the Osseointegration of Titanium Dental Implants

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Abstract: *Bone is a metabolically active tissue that renews itself throughout one's life. Osseointegration is a vital process in which characteristics of the implant like the macro and micro geometry, surface properties, etc. play an important role in modulating cellular and molecular behavior. The process of osseointegration depends on many factors but systemic biological irregularity is seldom considered as a cause for failure in osseointegration of titanium implant. Various nutrients may significantly impact certain parameters of bone remodeling and in turn affect osseointegration. Certain factors in particular, such as levels of vitamin D3, vitamin K, blood sugar and cholesterol are some of the main systemic factors in the host that can contribute or interfere significantly in the process of effective bone tissue formation and growth over the implant surfaces. This review aims to comprehend the significance of lipoproteins, vitamin D3, vitamin K and magnesium levels in optimizing the process of osseointegration around titanium implants.*

Key Word*: titanium implant, osseointegration, vitamin D, cholesterol, lipoproteins, magnesium, vitamin K, early failure, bone.*

Date of Submission: 16-04-2021 Date of Acceptance: 30-04-2021

I. Introduction

Dental implants have proven to be a predictable modality for replacing, missing and failing teeth, with several types of removable and fixed prosthesis. It is crucial that the implant gets integrated to the bone during its initial stages, which ensures clinically asymptomatic fixation prior to functional loading. Osseointegration of implants rely on various factors including implant characteristics, surgical factors, loading factors and even patient related factors[1]. Despite of the constant efforts to increase the survival rate of implants, there are some factors that still need to be considered before planning implant placement. The most common problem encountered in modern implantology is early failure of implants due to lack of osseointegration. Identification of some additional systemic risk factors may help reduce the failure rate and increase the predictability of dental implant treatment[2]. Therefore, in order to obtain a timely and effective osseointegration, the implant recipient as well as the bone must be absolutely healthy and in required cases, the patients should be provided with the necessary nutrients to facilitate peri-implant hard and soft tissue healing.

In the recent years, literature has been emphasizing the need for pre-surgical evaluation and optimization of vitamin D3, lipoproteins and vitamin K levels prior to implant surgery[3]. According to the studies, there is a close link between vitamin D3 and blood cholesterol levels. There are two major lipoproteins, HDL (also known as good cholesterol or high-density lipoprotein) and LDL (also known as bad cholesterol or low-density lipoprotein).

HDL facilitates bone synthesis; it also most likely has effects on reduced bone resorption. Particularly, decreased HDL levels result in enlarged adiposity of the bone marrow affecting the function of bone forming cells. Vitamin D3 plays an important role in the metabolism of bone and is considered to be linked to bone development hormones. Additionally, it decreases the potential effects of allergic and inflammatory reactions[3]. Whereas, vitamin K more precisely vitamin K2, beyond its role in the blood clotting cascade, plays a primary role in directing calcium to the bone. Vitamin K2 contributes to good bone health by maintaining calcium inside the bone thereby leading to better bone healing and osseointegration[4].

II. Bone Remodeling and Low Density Lipoproteins (LDL)

A great number of studies have indicated that high cholesterol level has significant impact on bone causing low bone density, volume and strength. Today it is accepted that there is a strong connection between bone cartilage homeostasis and lipid metabolism. A high cholesterol level is linked not only with the pathophysiology of atherosclerosis and osteoporosis but it has been linked to periodontal disease as well[5,6,7].

Cholesterol gets transported to the plasma primarily as cholesteryl esters in association with lipoproteins. Two types of lipoproteins exist- the good (HDL), and the bad (LDL)[3].

A rise in oxidized LDL circulating level induces alveolar bone loss[8,9] and is linked to the severity of local inflammatory reaction to bacteria; and also, the vulnerability of diabetic patients to periodontal diseases[10]. Osteoblasts can internalize, bind and process HDL3/LDL cholesterol. They can also selectively take up cholesteryl esters away from HDL and LDL[11]. At the cellular level, bone cells mainly osteoblast have the ability to oxidize low density lipoproteins thereby causing increase in the local concentration of oxidized reactive products inside the bone tissue. This induces successive harmful cellular effects on the density of bone and also inhibits bone cell differentiation with the help of bioactive lipids[12].

Krieger et al[13] established a rise in osteoclast numbers, osteoblastic activity inhibition and a reduced bone remodeling in hyperlipidemic rats. Luegmayr et al[14] reported that increased cholesterol levels may interfere with the bone remodeling process leading to decrease in bone mass through increased activity and differentiation of osteoclasts. Certainly, the Demer group disclosed that at the cellular level, hyperlipidemia lead to inhibition of alkaline phosphatase activity and osteogenic signaling which decreased the production of mature osteoblasts, a major molecular marker in the process of bone remodeling[15].

It has also been stated that hyperlipidemic conditions intensify osteoclastic activity[5] leading to increase in bone resorption[16]. This remarkably affects healing of the bone tissue thereby reducing bone volume and its surface[17]. Some studies have shown that high LDL impairs the processing and orientation of collagen[18] which decreases the integrity and quality of the bone. The deleterious effects on mineralization and formation of osteoblasts is due to reduction of bone strength, fracture toughness and bending strength induced by hyperlipidemia[17]. Additionally, it has been shown recently that oxidized LDL cholesterol encourages cell death through osteoblastic cell apoptosis[19]. It was confirmed by Hirasawa et al[11] that conditions like atherogenesis (high level of LDL) caused cell death. Furthermore, statins, which are cholesterol lowering drugs have been reported to increase differentiation and mineralization of osteoblasts, decrease osteoclast formation and improve the bone volume[20,21].

HDL (good cholesterol) on the other hand carries several antioxidants that may disrupt the cascade system of LDL oxidation[22]. Another vital HDL property is its capacity of inhibiting cell death induced by oxidized LDL. Particularly, it is conveyed that HDL hinders monocytic cell apoptosis by encouraging cholesterol efflux thereby averting cholesterol accumulation caused by the oxidized LDL[23]. HDL should therefore be considered protector of the bone cell.

III. Effect of Vitamin D on Bone

The most significant vitamin D related compound is vitamin D3 (cholecalciferol). Vitamin D modulates calcium and phosphate metabolism, it promotes growth, bone mineralization of the skeleton and teeth, and maintenance of normal bone and teeth. Vitamin D which is a steroid hormone, is obtained via diet or formed in the skin from cholesterol when there is adequate sun (ultraviolet light) exposure. Cholesterol is transformed into pre–vitamin D3 which is then isomerized to cholecalciferol. After vitamin D is bound to carrier protein, vitamin D3 is directed to the liver, where it is hydroxylated enzymatically by CYP27A1, forming 25-hydroxyvitamin D3 (calcidiol, or 25OHD3)[24].

Vitamin D3 works by stimulating osteoblast activity inside the bone and increases the extracellular matrix protein production by osteoblasts. In addition, vitamin D stimulates absorption of intestinal calcium and inhibits the synthesis and secretion of parathyroid hormones[25,26]. Lack of vitamin D3 may be caused from inadequate dietary consumption along with the insufficient sunlight exposure. Studies have repeatedly shown that most people in the northern hemisphere are deficient in Vitamin D3, such deficiency in these patients is connected to the catabolic turnover of bone and its main consequence is an increase in the occurrence of osteoporotic fractures[27]. This deficiency is also connected to slow or poor fracture or bone injury recovery [28,29]. These results support the role of the steroid hormone in the process of bone regeneration and turnover. Animal studies have shown, peri-implant bone formation to be significantly less in rats that are deficient in vitamin D3[30]. Dvorak et al[31], in their recent research indicated that lack of vitamin D3 has a undesirable effect on bone formation of cortical peri-implant bone in ovariectomized lab rats, which may be compensated by a diet rich in vitamin D3.

Deficiency in vitamin D has been implicated in numerous diseases such as diabetes, high blood pressure, cardiovascular diseases as well as several types of cancers. It has also been implicated in various dysregulation of the immune system and allergic disorders[26]. It is now known that cells from the immune system contain all the characteristics needed to convert 25-hydroxyvitamin D to active 1,25-dihydroxyvitamin D during a bacterial infection[31].

Our understanding of vitamin D3 metabolism and its biological effects has exponentially grown in the past years. It has also become evident that vitamin D has relevant and significant immunomodulatory effects. Ginde et al [32] stated that vitamin D deficiency is linked with a high prevalence of severe diseases in the

emergency department of the hospital. It was shown by Flynn that levels of Vitamin D3 <20 ng/mL has a substantial effect on the extent of hospital stay, infection rates and organ dysfunction[33].Therefore it is clear that optimal vitamin D3 not only plays an important role in bone repair and regeneration but also in the implant recipient immune response to infection.

Interestingly there is limited information available with regards to the effects and contribution of vitamin D3 supplementation on bone regeneration and around dental implant surfaces. In general, these studies propose that supplementation of vitamin D has positive results on bone turnover in the patients lacking vitamin D which might hold true for bone rejuvenation as well[26,30].

Supplemental recovery program: the science behind dental healing.

Owing to the impact of vitamin D deficiency-related complications and failures in dentistry, clinicians are advised to use vitamin D supplements when deficiency is observed. Typically, 5,000 IU/day is recommended by the AACE; however, an 8- to 12-week supplementation period is needed to reach adequate levels. This time frame makes implant dentistry quite inconvenient, owing to the often-encountered need to restore teeth at earlier time points, along with the necessity to satisfy patient expectations within reasonable time frames. Over the years, it has become increasingly clear that vitamin D absorption is further optimized with several co-factors. These include vitamin K, magnesium, calcium, manganese, and boron, among others. These co-factors, when present, help absorb vitamin D towards optimal level in shorter healing periods. Several supplementation recovery programs have been designed specifically for dentistry and implant with the aim of elevating levels prior to implant surgery within a 4-week period. Noteworthy research, however, has demonstrated that patients older than 65 years of age, diabetics, smokers, obese patients, and patients with reported compromised immune systems typically require double this time-frame of supplementation requirements[34].

IV. The Importance of Magnesium

Magnesium is one of the most abundant minerals found in the body. It plays a significant role as a modifier of the inflammatory and immune response[35]. Magnesium also maintains the homeostasis of minerals in the bone tissue and influences the crystal growth of hydroxyapatite and bone cell activity[36].

Research has shown that about 2.5 to 15% of the total world population exhibit low levels of serum magnesium (less than 1.46mg/dL)[37]. Various epidemiological studies prove hypomagnesemia as a possible risk factor for osteoporosis because of the strong link between low bone density, increased bone loss and magnesium deficient diet[38,39]. According to Rude et al[40], the results of animal studies show that magnesium deficiency caused loss of bone by affecting the volume of trabecular bone. The study also exhibited increased release of pro-inflammatory cytokines, changes in the parathyroid hormone activity and secretion causing decreased bone formation.

Bellucci et al[41], in his 2011 study found out that there is imbalance in turnover of the bone in magnesium deficient animals with more bone resorption than bone formation. He concluded that magnesium deficiency led to changes in bone metabolism causing lower cortical bone thickness and lower bone mineral density around titanium implants and also expressed lower removal torque of established osseointegrated implants.

Recently, it was explained by Uwitonze and Razzaque[42], that magnesium is an essential cofactor for vitamin D3 activation and synthesis. It is now well known that vitamin D3 is one of the most important hormones for bone growth and bone repair.

V. Vitamin K and Bone Quality

Vitamin K, a multifunctional vitamin, has now been proved to improve the bone turnover. Vitamin K also stimulates differentiation of osteoblasts, increases bone formation markers such as alkaline phosphatase, growth factors etc; and controls mineralization of extracellular matrix by Y-glutamyl carboxylation. As shown in literature, vitamin K inhibits apoptosis of osteoblasts and reduces differentiation of osteoclasts thereby preventing bone resorption[43].

Vitamin K naturally falls into 2 types: vitamin K1 and vitamin K2. Vitamin K2 (menaquinone) refers to the group of chemical compounds with specific formulation. Two Vitamin K2 forms, menoquinone-4 (MK-4) and menoquinone-7 (MK-7) have been used as nutritional supplements to support bone health[44].

A study by Murasawa et al[45] on ovariectomized rats (given MK-7;30 mg/kg bw per day for 5 months) observed substantial decrease in bone mineral density compared to sham-operated rats. MK-7 acted against this decrease by only enhancing the bone strength. This benefit was believed to occur due to maintainence and development of bone quality rather than by increasing the density of bone mineral. It has been demonstrated that MK-7 stimulates bone formation by activating osteoblastogenesis[46] and decreases resorption of bone by suppressing osteoclastogenesis[47] through inhibition of NF- κ B activation[48].

MK-4 not only carboxylates and activates osteocalcin (bone specific protein formed by osteoblasts); but also increases the accumulation of collagen[49]. This finding was confirmed in a study that proved MK-7 increases the production of collagen with the help of osteoblasts. Collagen inhabits over half the bone volume and forms the foundation wherein calcium plus other minerals assemble. This collagen buildup contributes to the elasticity and flexibility of the bone. Thus, accumulation of collagen plays a vital role in good quality bone formation together with calcium and other minerals.

Many observational studies have shown a strong correlation between bone metabolism, fracture of bone and vitamin K intake. These studies concluded that increased consumption of vitamin K could lessen osteoporosis risk and improve the quality of bone[50,51].

VI. Proposed Biological Protocol for Improvement in Implant Osseointegration

Many protocols have been developed by different groups that suggest to improve implant osseointegration and achieve optimum bone healing during the process of tooth replacement with titanium implants. These protocols suggested that the following factors should be optimized and supplemented prior to and after implant placement.

1. For the desirable LDL levels, the blood cholesterol should be under 100mg/dL.
2. For the optimal levels of vitamin D3, serum levels should be in the range of 30-50ng/mL.
3. The average accepted value of RBC magnesium is 3.8 to 6.0mg/dL.
4. Ratio of vitamin D3 to vitamin K2 should be 10000 IU of vitamin D3 to 100ug of vitamin K2.
5. A four week pre and post-surgery administration of 50000 IU(weekly) of vitamin D3 is recommended.

For titanium implants to maintain the osseointegration and to remain functional for a long time, the patients need to follow and maintain the blood cholesterol, vitamin K and vitamin D3 levels for the rest of their lives. Comparatively, lesser number of investigational studies have tried to explore the effects of vitamin D3 on osseointegration of dental implants. It should be remembered that various nutrients work synergistically with other nutrients and in the specific case of vitamin D3, magnesium level also needs to be monitored and optimized to stimulate the activation of vitamin D3.

Many studies seem to show a positive effect of vitamin D on osseointegration, though it is not yet completely clear as to whether the supplementation would encourage peri-implant healing of the bone tissue in cases of post-integration bone loss. High LDL level causes decrease in bone metabolism, alkaline phosphatase inhibition and increase in fat tissue inside the bone. This leads to lesser growth and poor healing of bone compromising the osseointegration process. Statins help in the reduction of inflammatory conditions and decreases the levels of LDL cholesterol; however; studies have exhibited that optimal levels of vitamin D3 naturally reduces the elevated LDL levels and improves bone healing and health. Vitamin K effect on bone tissue may have no connection to cause changes in the density of the bone mineral or in the bone turnover but it does have an impact on the quality of bone as it is known to accumulate calcium inside the bone tissue. Aside from their individual roles, a synergistic action between vitamin D and K takes place and has a significant role in the process of bone healing, osseointegration and even patient's general health and well-being.

VII. Conclusion

The titanium surface treatment and enhancement technology is complex but has achieved great success even in unhealthy bone. Titanium implant with coatings or advanced subtractive and additive surface treatment seem to perform better and appear to be less sensitive to unhealthy bone. Depending on the roughness and hydrophilicity of the implant surface, bone forming cells attach readily and initiate the process of osseointegration. However, the lack of certain nutrients could result in early implant failure and also have a negative impact on host acceptance of the bone graft. We propose to examine serum levels of vitamin D (prescription recommendation : 25-hydroxy vitamin D equals to ergocalciferol and cholecalciferol), LDL cholesterol (prescription recommendation : total cholesterol i.e, HDL and LDL), red blood cell magnesium level (RBC magnesium level) and serum vitamin K levels; methodically prior to placement of titanium implants to ensure their optimal levels in the patient which would lead to favorable bone healing and osseointegration. Clinicians should pay utmost attention when prescribing for magnesium levels as the RBC magnesium values are more accurate than the serum levels. Optimal levels of these factors would lead to improvement in the patient outcome and also increase the longetivity of the titanium implants. Abnormal values of these nutrients can lead to serious bone dysfunctions and adversely affect the metabolism of the bone. Hence, it is important to rectify these anomalies prior to surgical placement of titanium implants. Additional multicentric studies would be helpful in establishing a firm link between vitamin D3, cholesterol, magnesium and vitamin K levels with the biological stability and long term success of titanium implants. Further studies would also help in instituting protocols and dosages of the above mentioned factors; prior to, during and after implant placement.

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Kreena Shah, et. al. "The Role and Importance of Lipoproteins, Vitamin D3, Vitamin K and Magnesium in the Osseointegration of Titanium Dental Implants."*IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 20(04), 2021, pp. 11-16.